

Cell Therapy and Angiogenesis (TCTAP A-154 to TCTAP A-157)

TCTAP A-154

Intracoronary Infusion of Bone Marrow-derived Selected CD34+CXCR4+ Cells and Non-selected Mononuclear Cells in Patients with Acute STEMI and Reduced Left Ventricular Ejection Fraction. Extended 6-year Follow-up of Randomized, Multicenter REGENT Trial

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Background: Comparison of intracoronary infusion of bone marrow (BM)-derived unselected mononuclear cells (MNC) and selected CD34+CXCR4+ cells (CXCR4) in acute myocardial infarction (MI) and reduced <40% left ventricular ejection fraction (LVEF) assessed by MRI.

Methods: Bone marrow was harvested from iliac crest. MNC were isolated by Ficoll gradient and CD34+CXCR4+ by immunomagnetic selection. **METHODS:** 200 patients were randomized to intracoronary infusion of MNC (n=80) or CD34CXCR4 (n=80) BM cells or to the control (CTRL) without BM cell treatment. Primary endpoint: change of LVEF and volumes measured by MRI before and 6 months after the procedure.

Results: Primary end-point: After 6 months LVEF increased by 3% (p=0.01) in MNC, 3% in CD34CXCR4 (p=0.04) and remained unchanged in CTRL groups (p=0.73). There were no significant differences in absolute changes of LVEF between the groups. Absolute changes of LVESV and LVEDV were not significantly different in all groups. Significant increase of LVEF was observed only in patients treated with BM cells who had baseline LVEF < median (37%). Baseline LVEF < median and time from the onset of symptoms to primary PCI ≥ median were predictors of LVEF improvement after BMC therapy. There were no differences in MACE (death, reinfarction, stroke, TVR) between groups at 6 months. After 6 years no differences in death (Kaplan-Meier, p=0.82), MI (p= 0.445), death/MI/stroke (p=0.914) and death/MI/heart failure (p=0.712) were found.

Conclusion: In patients with acute MI and impaired LVEF treatment with BM cells does not lead to a significant improvement of LVEF or volumes. There was a trend in favor of cell therapy in patients with most severely impaired LVEF. Long term follow-up confirmed the safety of the cell therapy.

TCTAP A-155

Co-injection Basic Fibroblast Growth Factor for Adipose Derived Stem Cells Transplantation: Improved Cardiac Remodelling and Function of Myocardial Infarction

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Background: The cell-based therapy can improve the cardiac function but is limited by the survival within the ischemic tissues. The injectable cardiac tissue engineering aims to support cell-based therapies and enhance their efficacy for cardiac diseases. So far, no research is devoted to studying the usefulness of the combination of bFGF and adipose-derived stem cells (ADSCs) to treat myocardial infarction.

Methods: Adipose derived stem cells (ADSCs) were isolated from subcutaneous adipose tissues. The ADSCs were induced to differentiate into adipocytes, osteoblasts, and cardiac myocyte in vitro. bFGF was then co-injected with ADSCs into the left ventricular wall of rat infarction models. The structure and functional consequences of transplantation was determined by detailed histological analysis and echocardiography.

Results: After injection four weeks later, graft size were significantly higher and larger in the bFGF + ADSCs group than the PBS + ADSCs group and PBS + bFGF (p < 0.05). The ADSCs could differentiate into cardiomyocytes, endothelial cells and vascular smooth muscle cells *in vivo*. The arteriole densities within the infarcted area improved significantly in the bFGF + ADSCs group compared with those in the PBS + ADSCs group and PBS + bFGF4 weeks after transplantation (p < 0.05). In addition, Quantitative analysis showed that the percentage of fibrotic areas was significantly lower in PBS + ADSCs and bFGF + ADSCs groups than that in the PBS only group and PBS + bFGF group (p < 0.05).

Conclusion: Combined use of bFGF and ADSCs transplantation may significantly increased the number of arterioles, reduced the infarcted size, attenuated ventricular remodeling and improved cardiac function.

TCTAP A-156

Retrograde Coronary Vein Delivery of Basic Fibroblast Growth Enhances Bone Marrow Mesenchymal Stem Cells Engraftment for Myocardial Repair in a Canine Infarct Model

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Background: Retrograde coronary venous delivery of basic fibroblast growth factor (bFGF) or bone marrow mesenchymal stem cells (MSCs) have been demonstrated to target infarcted myocardium. The present study aimed to investigate the effects of bFGF on MSCs engraftment via coronary vein infusion and their combined efficacy for myocardial repair in a canine model of myocardial infarction.

Methods: Under hypoxic conditions, the migration capacity was assessed in MSCs cultured with bFGF, vascular endothelial growth factor or insulin-like growth factor. For *in vivo* experiments, dogs underwent ligation of left anterior descending coronary artery to create myocardial infarction (MI). After one week, combined bFGF (200 ng/mL) and MSCs (1×10^6 cells) (n = 5), MSCs alone (1×10^6 cells, n = 5), bFGF alone (200ng/mL, n = 5), or placebo (phosphate-buffered saline, n = 3) was retrogradely infused into anterior interventricular vein. Serial echocardiography studies were performed at baseline, 1 week after MI (before infusion) and 4 weeks after infusion. Then, hearts were harvested for histology analysis.

Results: The number of migrated cells was higher in MSCs cultured with bFGF compared with other growth factors *in vitro*. Four weeks after treatment, left ventricular ejection fraction was significantly better in the bFGF/MSCs and MSCs alone group (both p < 0.05 versus control group). However, the radial strain value of the infarct border area was improved only in the combination-treated group, accompanied by greater infarct size reduction (p < 0.05). Immunofluorescence showed that bFGF significantly increased retention of the enhanced green fluorescence protein-labeled MSCs in the infarcted area, with enhanced cell differentiation into myocardiocytes and vessels (all p < 0.05).

Conclusion: Retrograde coronary vein infusion of bFGF promotes MSCs engraftment in the infarcted myocardium, accompanied by enhanced angiogenesis. Combination of bFGF with MSCs restores cardiac function and regional contractility, with greater infarct size reduction. Our findings suggest a novel strategy for cardiac repair after myocardial injury.

TCTAP A-157

Retrograde Coronary Vein Infusion Achieves Targeted Cell Engraftment into Infarcted Myocardium for Cardiac Repair

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Background: Cell transplantation has emerged as a promising treatment for cardiac repair after myocardial infarction. However, efficient cell delivery to the targeted myocardium remains a practical challenge. This study evaluated the efficiency of mesenchymal stem cells (MSCs) delivery via coronary veins and examined cell engraftment and differentiation in a canine infarct model.

Methods: Dogs (n = 12) underwent ligation of left anterior descending (LAD) coronary artery to create myocardial infarction (MI). After one week, the coronary sinus was cannulated and an over-the-wire balloon catheter was advanced to the mid-portion of anterior interventricular vein (AIV) in parallel to LAD. The balloon catheter was inflated temporarily to occlude the AIV, and 1×10^8 enhanced green fluorescence protein (EGFP)-labeled mesenchymal stem cells (MSCs) were injected into the AIV. The animals were euthanized at 1 (n = 4), 7 (n = 4), and 14 (n = 4) days post-delivery. The hearts were harvested for histology analysis.

Results: Cell delivery by retrograde coronary venous perfusion was successful in 100% (12/12) of the animals. No death, cardiac tamponade, or sustained arrhythmia events occurred during the procedure or the follow-up periods. The average number of EGFP+ cells was dramatically higher in the LAD territory than in the remote left circumflex territory at each timepoint (221 ± 24 versus 15 ± 6 cells/mm² at 1 day, 306 ± 42 versus 16 ± 5 cells/mm² at 7 days, 262 ± 24 versus 9 ± 3 cells/mm² at 14 days) (all p < 0.05). Notably, a more homogeneous distribution of EGFP+ cells was observed in all slides of the LAD region. In addition, we found cardiac troponin I and α -smooth muscle actin expression in EGFP+ cells, indicating the differentiation of MSCs into cardiomyocytes and arterioles.

Conclusion: Regional cell delivery is safe and feasible through coronary venous system. Infusion of MSCs via the coronary veins provides targeted and homogeneous cell engraftment into the infarcted myocardium for cardiac repair.